

5 protein that mediates secretion, a kinase, a G-protein, a  
cell surface receptor, a GTPase activating protein, a  
guanine nucleotide exchange factor, a phosphatase, a  
protease, a phosphodiesterase, a bacterial protein toxin,  
an importin, an RNA-binding protein, an SCF complex  
10 component, an adherin, or a protein encoded within a  
biosynthetic cluster. In certain other embodiments of the  
fourth aspect, the variant regulator protein is selected  
to have more activity in a heterologous cell and/or more  
activity in a homologous cell. In certain embodiments,  
15 the variant regulator protein is selected to have more  
activity in a heterologous cell and/or more activity in a  
homologous cell and to cause more secondary metabolite to  
be produced in a homologous cell and/or a heterologous  
cell when compared to the cognate, wild-type regulator  
20 protein. In a particularly preferred embodiment, the  
variant regulator protein is a lovE variant regulator  
protein.

In a fifth aspect, the invention provides an isolated  
variant regulator protein of secondary metabolite  
25 production having increased activity compared to a  
cognate, wild-type protein, the variant regulator protein  
made by the process comprising: (a) selecting a nucleic  
acid comprising a polynucleotide encoding a protein  
regulator of secondary metabolite production; (b) mutating  
30 the nucleic acid to create a plurality of nucleic acid  
molecules encoding variant regulator proteins of secondary  
metabolite production; (c) selecting a variant regulator  
protein with more activity than the cognate, wild-type  
protein; and (d) recovering the selected variant regulator  
35 protein.

In certain embodiments of the fifth aspect, the  
secondary metabolite is a fungal secondary metabolite. In  
certain embodiments of the fifth aspect, the protein  
regulator of secondary metabolite production is a  
40 transcription factor. In certain embodiments of the fifth  
aspect, the protein regulator of secondary metabolite

5 production is a transmembrane transporter, a protein that  
mediates secretion, a kinase, a G-protein, a cell surface  
receptor, a GTPase activating protein, a guanine  
nucleotide exchange factor, a phosphatase, a protease, a  
phosphodiesterase, a bacterial protein toxin, an importin,  
10 an RNA-binding protein, an SCF complex component, an  
adherin, or a protein encoded within a biosynthetic  
cluster. . In certain embodiments of the fifth aspect,  
the variant regulator protein has more activity in a  
heterologous and/or a homologous cell than the cognate,  
15 wild-type protein. In certain embodiments of the fourth  
aspect, the variant regulator protein increases production  
of a secondary metabolite in a heterologous cell and/or a  
homologous cell when compared to the cognate, wild-type  
protein. In a particularly preferred embodiment, the  
20 variant regulator protein is a lovE variant regulator  
protein.

In a sixth aspect, the invention provides a fungus  
having improved lovastatin production made by the process  
of transforming a fungal cell with a nucleic acid molecule  
25 encoding a lovE variant protein of the first aspect of the  
invention. In an embodiment thereof, the nucleic acid  
molecule is selected from a nucleic acid molecule of the  
second aspect of the invention.

In a seventh aspect, the invention provides an  
30 improved process for making lovastatin comprising  
transforming a fungal cell with a nucleic acid molecule  
encoding a variant of the lovE protein of the first aspect  
of the invention. In an embodiment thereof, the fungal  
cell is transformed with a nucleic acid molecule of the  
35 second aspect of the invention.

In a eighth aspect, the invention provides a nucleic  
acid molecule encoding a lovE protein defined by SEQ ID  
NO:91. In an embodiment thereof, the invention provides  
an isolated lovE nucleic acid molecule defined by SEQ ID  
40 NO:92.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a photographic representation of cells growing on media with and without G418 selection demonstrating *lovFp-HIS3p-Neo* activation in *S. cerevisiae*. Controls include MB968 (vector only), MB2478 (lowly expressed wild-type *lovE*), and MB1644 (highly expressed wild-type *lovE*). All *lovE* variants are expressed in an MB968 vector backbone similar to MB2478.

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Figure 2A is a graphic representation of *lovFp-CYC1p-lacZ* expression in *S. cerevisiae* strains expressing *lovE* variant proteins from the clones *lovE* 1-10.

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Figure 2B is a graphic representation of *lovFp-CYC1p-lacZ* expression in *S. cerevisiae* strains expressing *lovE* variant proteins from the clones *lovE* 1-10 from a separate transformation than that of Figure 2A.

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Figure 3 is a graphic presentation of *lovFp-CYC1p-lacZ* expression in *S. cerevisiae* strains expressing *lovE* variant proteins from clones *lovE* 16-41.

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Figure 4 is a graphic presentation of *lovFp-lacZ* expression in *S. cerevisiae* strains expressing *lovE* variant proteins from clones *lovE* 1-10.

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Figure 5 is a graphic presentation of *lovFp-lacZ* expression in *S. cerevisiae* strains expressing *lovE* variant proteins from clones *lovE* 16, 20, 21, 30-34, and 36-41.

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Figure 6 is a graphic presentation of lovastatin culture concentration, as measured by enzyme inhibition assay, from broths of *A. terreus* cultures expressing *lovE* variant proteins 1-10 in.

Figure 7A is a graphic depiction of lovastatin culture concentration, as measured by HPLC analysis, from